

Rima Matsumoto—Nonalcoholic Steatohepatitis (NASH)

In early 2000, 27-year-old Rima Matsumoto began to think that there was something wrong with her health. She had put on weight and—for no obvious reason—she began feeling tired, lacking energy and stamina. “It wasn’t like me,” says the upbeat marketing director of a Washington, DC-based nonprofit organization. “I’m a very active person who enjoys playing sports.” Indeed, between the ages of 5 and 15 she was an avid and competitive gymnast and weighed about 90 pounds. She had to give that up, however, when she graduated from college. “I became much more sedentary, wasn’t eating good food the way I used to, and started to gain weight, but nothing major,” says Rima.

What Rima didn’t know at the time was that, along with the weight gain, she had developed a liver disease known as nonalcoholic steatohepatitis or NASH. NASH is marked by fat accumulation in and inflammation of the liver. It resembles alcoholic liver disease in many ways, but—as its name implies—it occurs in people who drink little or no alcohol.

After feeling tired and lethargic for six months of 2000, Rima said her health started to affect her personal life. “I didn’t want to go out or socialize with friends,” she says. “I felt like staying home all the time.” She felt depressed and began putting on even more weight. During this period, Rima’s liver enzymes, which were being monitored by her doctor, continued to rise—a sign of liver abnormality. By this time, Rima says, she was extremely frustrated. “It was affecting my work and my relationship with my boyfriend.” In August 2001, after seeing a specialist and undergoing several more blood tests, Rima was evaluated by the Liver Diseases Section of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). A biopsy of her liver was taken, and it was then that she learned that she had NASH.

ABOUT NONALCOHOLIC STEATOHEPATITIS (NASH)

The underlying causes of NASH are unclear. The

condition is most common in adults over the age of 40 who are overweight or have diabetes, insulin resistance, or elevated levels of fat in their blood. In fact, the “typical” patient with NASH is a middle-aged woman who is overweight and diabetic. As Rima’s profile shows, however, it is possible for NASH to develop in the presence of only mild weight gain and in the absence of overt diabetes. In such cases, individuals often exhibit an impaired ability to respond to insulin coupled with impaired glucose tolerance (IGT), a dysfunction in the metabolism of the sugar. IGT is particularly insidious because it is often silent and may not be detected until it progresses to overt type 2 diabetes.

Although most people with NASH do not have any symptoms, a great danger of this disease is that it can lead to a cirrhotic liver, a condition in which the liver contains extensive fibrosis that stiffens blood vessels and distorts the internal structure of the liver. Over time NASH can lead to significant scarring of the liver in 30 percent of patients and liver cirrhosis in 10 to 15 percent. Liver cirrhosis is irreversible and may progress to liver failure, ultimately requiring liver transplantation.

PARTICIPATION IN NIDDK CLINICAL RESEARCH

At the time of her referral to NIDDK, Rima weighed approximately 130 pounds. On her 5' 1" frame, this placed her Body Mass Index (BMI) at 25.5: just barely overweight (Note: For a discussion of BMI, how it is used, and other ways to measure body weight, see the sidebar “Who Should Lose Weight?”). She was also insulin resistant, a pre-diabetic condition that often leads to the subsequent development of frank diabetes. Therefore, while Rima does not fit the “classic” profile of a patient with NASH in that she is young and is not diabetic, her condition highlights how NASH can strike beyond its traditional clinical bounds. Even small amounts of extra weight—in the presence of other factors such as insulin resistance and IGT—can predispose some people to NASH. Doctors are increasingly

PATIENT PROFILE

appreciative of the fact that the disease can occur in persons who are not obese or overtly diabetic and in children as well.

At the NIH Clinical Center, Rima is now enrolled in an NIDDK pilot clinical research study to evaluate the effectiveness of an experimental anti-diabetes medication that acts to improve the sensitivity of the body to insulin. “The clinical trial in which Rima is taking part is a preliminary study. If this medication proves itself to be safe and appears beneficial in improving liver histology, a larger controlled trial will be conducted,” says NIDDK research physician Kittichai Promrat, M.D., who is treating Rima for her disease as part of the NIDDK’s research efforts.

Rima takes the experimental medication as a capsule once a day, first thing in the morning, and says she is responding well to the medication. Aside from minor headaches, she says she experiences no other side effects and is able to go on with her life as always. “I feel better now,” says Rima, “knowing I wasn’t making anything up and actually had a diagnosable disease. It relieved a lot of my anxiety.”

“My doctors tell me that although I am not diabetic, I am insulin resistant, and that if I don’t take care of myself I could become diabetic. They say the most important things for me to do are to watch my diet, lose weight, and exercise.”

HISTORY OF NASH

NASH was recognized as a specific medical condition in 1980. Up to that point, it was considered rare and was referred to simply as fatty liver, fatty hepatitis, or diabetic hepatitis. Today, it is believed that NASH is becoming more and more common in the U.S., most likely as a result of the epidemic increase in obesity. In fact, NASH may affect as many as 5 percent of Americans. It often goes undiagnosed because it causes few symptoms and—when symptoms do occur—they are often vague and non-specific, such as fatigue.

Historically, people with severe cases of NASH were thought to be alcoholics, even when they denied drinking excessively. Since 1980, however, it has become clear that this disease is relatively common and it is not related to drinking alcohol. Rima, for example, says “I don’t really drink alcohol except on special occasions or holidays, and only a glass of wine at most.”

CURRENT DIAGNOSIS AND TREATMENT METHODS

Usually, NASH is initially suspected on the basis of abnormal liver enzymes detected as part of a routine blood test. Further indication of the disease comes from ultrasound examination of the abdomen: a “bright” liver is indicative of elevated levels of fat in the organ. NASH is confirmed if a liver biopsy shows fat, inflammation, and injury. It is important to note that patients with mild elevations in liver enzymes and a bright liver on ultrasound may have no injury to the liver. For these patients, the only way to separate “simple fatty liver” from NASH is by liver biopsy.

Currently, there is no established treatment specific for NASH. Therapies focus on strategies designed to reduce weight and improve the symptoms of diabetes, either through changes in diet and exercise or with drugs. NASH patients who are obese, diabetic and with high lipids in their blood are advised to lose weight and to control their diabetes and elevated lipids. “Many patients benefit just by knowing about the disease and

NEW NIDDK INITIATIVE TO COMBAT NASH

In addition to the pilot clinical study in which Rima is participating, the NIDDK is undertaking a new initiative to establish an interlocking network of cooperative investigators, who will design and implement a database and clinical research network to study the causes, contributing factors, natural history, complications, and therapy of this disease.

working on diet and exercise,” says Dr. Promrat. He adds that patients are susceptible to NASH at different levels of obesity, “and some patients, quite frankly, are not obese at all,” he adds. Rima’s weight, for example, is now 136 pounds, considered slightly overweight for her height, but not obese. She is seeing a dietitian as part of her treatment. She is also aware that there is a history of diabetes on her mother’s side of the family. “My doctors tell me that although I am not diabetic, I am insulin resistant, and that if I don’t take care of myself I could become diabetic.” Thus, although Rima does not fit the typical clinical profile for NASH, her disease may be indicative that the conventional profile is expanding.

LIVING WITH THE DISEASE

Rima says that since she’s been in the NIDDK protocol, she has had more energy and—though she says she has her good days and bad—generally feels much better. “I’m so glad I was recommended to NIDDK and qualified for the protocol,” she says. But she’s also under no delusions. “My doctor works closely with me, but I know that with my disease I need to do a lot of the work myself, namely watch my diet, lose weight and exercise. I need to take responsibility for my life.”

Rima credits a loving support system of family and friends, and especially her boyfriend, with helping her get through the hard times. “If it wasn’t for this understanding and support, I think I would’ve given up even before coming to NIDDK,” she says.

NONALCOHOLIC STEATOHEPATITIS (NASH) FACTS

- **As many as 5 percent of Americans may be affected to some degree by NASH.**
- **NASH is marked by accumulation of fat in the liver associated with inflammation and liver cell injury, which, in a proportion of patients, can lead to severe liver damage.**
- **NASH is not connected with other causes of liver disease, including hepatitis B and C viruses, autoimmune disorders, alcohol, drug toxicity, or the accumulation of copper or iron.**
- **There is no known specific cause of NASH and there are no universally agreed-upon treatments for it. Therefore, approaches to treating NASH typically involve drugs to improve the underlying insulin resistance and impaired glucose tolerance as well as changes in diet and exercise to promote weight loss.**
- **NASH can be a silent disease; many affected people are unaware of their condition because they feel well and have no overt clinical symptoms of liver disease.**